

## DIRECTIONS FOR USE – USA

### JUVÉDERM VOLBELLA® XC

**Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed practitioner.**

**BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.**

#### 1. DEVICE DESCRIPTION

JUVÉDERM VOLBELLA® XC injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of cross-linked hyaluronic acid (HA) produced by *Streptococcus* species of bacteria, formulated to a concentration of 15 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

#### 2. INTENDED USE/INDICATIONS

JUVÉDERM VOLBELLA® XC injectable gel is indicated for injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21.

#### 3. CONTRAINDICATIONS

- JUVÉDERM VOLBELLA® XC is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- JUVÉDERM VOLBELLA® XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- JUVÉDERM VOLBELLA® XC contains lidocaine and is contraindicated for patients with a history of allergies to such material.

#### 4. WARNINGS

- The product must not be injected into blood vessels. Introduction of JUVÉDERM VOLBELLA® XC injectable gel into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft-tissue fillers, for example, after insertion of the needle, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly, and apply the least amount of pressure necessary. Rare, but serious, adverse events associated with the intravascular injection of soft-tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care professional specialist should an intravascular injection occur (see HEALTH CARE PROFESSIONAL INSTRUCTIONS #12).

- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled.
- Injection site responses consist mainly of short-term inflammatory symptoms starting early after treatment and lasting  $\leq 30$  days. Refer to the ADVERSE EVENTS section for details.

## 5. PRECAUTIONS

- JUVÉDERM VOLBELLA® XC injectable gel is packaged for single-patient use. Do not resterilize. Do not use if package is opened or damaged.
- In order to minimize the risks of potential complications, this product should only be used by health care professionals who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- Health care professionals are encouraged to discuss all potential risks of soft-tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- Based on preclinical studies, patients should be limited to 20 mL of any JUVÉDERM® injectable gel per 60 kg (130 lbs) body mass per year. The safety of injecting greater amounts has not been established.
- The safety and effectiveness for the treatment of anatomic regions other than the lips and perioral area have not been established in controlled clinical studies.
- Injection of more than 6.0 mL of JUVÉDERM VOLBELLA® XC injectable gel has not been studied for lip augmentation and correction of perioral rhytids.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- JUVÉDERM VOLBELLA® XC injectable gel is to be used as supplied. Modification or use of the product outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product.
- The safety for use during pregnancy, in breastfeeding females, or in patients under 22 years has not been established.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- JUVÉDERM VOLBELLA® XC injectable gel should be used with caution in patients on immunosuppressive therapy.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin) may, as with any injection, experience increased bruising or bleeding at injection sites.
- Patients may experience late onset adverse events with use of dermal fillers, including JUVÉDERM VOLBELLA® XC. Refer to ADVERSE EVENTS section for details.
- After use, treatment syringes and needles are biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.
- JUVÉDERM VOLBELLA® XC injectable gel is a clear, colorless gel without visible particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe; notify Allergan Product Support at 1-877-345-5372.
- JUVÉDERM VOLBELLA® XC should only be used by health care professionals who have appropriate experience and who are knowledgeable about the anatomy and the product for use in the lips and

perioral area.

- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with JUVÉDERM VOLBELLA® XC, there is a possible risk of eliciting an inflammatory reaction at the implant site. An inflammatory reaction is also possible if the product is administered before the skin has healed completely after such a procedure.
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the LUER-LOK® and needle hub connection.

## **6. ADVERSE EVENTS**

### **A. US Pivotal Study of JUVÉDERM VOLBELLA® XC**

In the multicenter, double-blind, randomized, controlled clinical trial to evaluate the safety and effectiveness of JUVÉDERM VOLBELLA® XC versus *Restylane-L*® (control) for lip augmentation and correction of perioral rhytids, subjects were randomized and treated in a 3:1 ratio with either JUVÉDERM VOLBELLA® XC (N = 168) or control (N = 56).

Subjects used preprinted diary forms to record specific signs and symptoms of injection site responses (ISRs) experienced during the 30 days after initial treatment, touch-up treatment (if performed), and repeat treatment. Subjects were instructed to rate each ISR listed on the diary as Mild, Moderate, Severe, or None.

- Mild ISRs were defined as awareness of sign or symptom but easily tolerated.
- Moderate ISRs were defined as discomfort enough to cause interference with usual activity.
- Severe ISRs were defined as incapacitating with inability to work or do usual activity.

The severity and duration of all ISRs reported by > 5% of subjects who completed post-treatment diary forms after initial treatment are summarized in Table 1 and Table 2, respectively. Table 3 shows the severity and duration of all ISRs after repeat treatment reported by > 5% of subjects. The majority of ISRs were mild or moderate in intensity, and their duration was short lasting (30 days or less). There were no significant differences in ISRs reported between JUVÉDERM VOLBELLA® XC and control. The incidence, severity, and duration of ISRs reported after the touch-up and repeat treatments were generally lower than those reported after initial treatment.

**Table 1. Injection Site Responses by Severity After Initial Treatment  
Occurring in > 5% of Treated Subjects**

Injection Site Responses	JUVÉDERM VOLBELLA® XC				Control			
	Total % (n/N <sup>a</sup> )	Mild <sup>b</sup> %	Moderate <sup>b</sup> %	Severe <sup>b</sup> %	Total % (n/N <sup>a</sup> )	Mild <sup>b</sup> %	Moderate <sup>b</sup> %	Severe <sup>b</sup> %
Any ISR	97.4% (150/154)	14.7%	45.3%	40.0%	98.0% (50/51)	8.0%	44.0%	48.0%
Swelling	92.9% (143/154)	23.1%	49.7%	27.3%	98.0% (50/51)	16.0%	46.0%	38.0%
Tenderness	89.6% (138/154)	53.6%	32.6%	13.8%	92.2% (47/51)	23.4%	66.0%	10.6%
Firmness	89.0% (137/154)	32.8%	48.2%	19.0%	92.2% (47/51)	25.5%	59.6%	14.9%
Bruising	89.0% (137/154)	35.0%	40.9%	24.1%	90.2% (46/51)	30.4%	47.8%	21.7%
Lumps/Bumps	87.7% (135/154)	43.0%	42.2%	14.8%	90.2% (46/51)	30.4%	52.2%	17.4%
Redness	83.1% (128/154)	47.7%	39.1%	13.3%	88.2% (45/51)	40.0%	44.4%	15.6%
Pain	80.5% (124/154)	58.9%	30.6%	10.5%	92.2% (47/51)	42.6%	46.8%	10.6%
Discoloration	41.6% (64/154)	54.7%	34.4%	10.9%	49.0% (25/51)	40.0%	36.0%	24.0%
Itching	30.5% (47/154)	76.6%	17.0%	6.4%	37.3% (19/51)	63.2%	36.8%	0%
Dryness	5.2% (8/154)	37.5%	37.5%	25.0%	3.9% (2/51)	0%	50.0%	50.0%

<sup>a</sup> N denotes the number of subjects who recorded responses in the diaries after initial treatment.

<sup>b</sup> Maximum reported severity in the diary. The percentages by severity are based on the number of subjects with the corresponding injection site response.

**Table 2. Injection Site Responses by Duration After Initial Treatment  
Occurring in > 5% of Treated Subjects**

Injection Site Responses	JUVÉDERM VOLBELLA® XC					Control				
	Total % (n/N <sup>a</sup> )	1-3 Days <sup>b</sup> %	4-7 Days <sup>b</sup> %	8-14 Days <sup>b</sup> %	15-30 Days <sup>b</sup> %	Total % (n/N <sup>a</sup> )	1-3 Days <sup>b</sup> %	4-7 Days <sup>b</sup> %	8-14 Days <sup>b</sup> %	15-30 Days <sup>b</sup> %
Any ISR	97.4% (150/154)	9.3%	30.0%	20.0%	40.7%	98.0% (50/51)	6.0%	44.0%	8.0%	42.0%
Swelling	92.9% (143/154)	46.9%	34.3%	13.3%	5.6%	98.0% (50/51)	42.0%	36.0%	12.0%	10.0%
Tenderness	89.6% (138/154)	47.8%	29.0%	15.2%	8.0%	92.2% (47/51)	31.9%	36.2%	25.5%	6.4%
Firmness	89.0% (137/154)	39.4%	27.0%	18.2%	15.3%	92.2% (47/51)	29.8%	40.4%	10.6%	19.1%
Bruising	89.0% (137/154)	32.8%	49.6%	13.9%	3.6%	90.2% (46/51)	26.1%	65.2%	8.7%	0%
Lumps/Bumps	87.7% (135/154)	24.4%	25.2%	17.0%	33.3%	90.2% (46/51)	32.6%	23.9%	4.3%	39.1%
Redness	83.1% (128/154)	65.6%	28.1%	5.5%	0.8%	88.2% (45/51)	57.8%	35.6%	6.7%	0%
Pain	80.5% (124/154)	75.8%	18.5%	4.8%	0.8%	92.2% (47/51)	61.7%	31.9%	6.4%	0%
Discoloration	41.6% (64/154)	64.1%	26.6%	6.3%	3.1%	49.0% (25/51)	68.0%	20.0%	4.0%	8.0%
Itching	30.5% (47/154)	72.3%	17.0%	8.5%	2.1%	37.3% (19/51)	78.9%	21.1%	0%	0%
Dryness	5.2% (8/154)	37.5%	0%	37.5%	25.0%	3.9% (2/51)	0%	50.0%	0%	50.0%

<sup>a</sup> N denotes the number of subjects who recorded responses in the diaries after initial treatment.

<sup>b</sup> Maximum duration reported in the diary. The percentages by duration are based on the number of subjects with the corresponding injection site response.

**Table 3. Injection Site Responses by Severity and Duration After Repeat Treatment with JUVÉDERM VOLBELLA® XC Occurring in > 5% of Treated Subjects**

Injection Site Response	Total % (n/N <sup>a</sup> )	Severity <sup>b</sup>			Duration <sup>c</sup>			
		Mild %	Moderate %	Severe %	1-3 Days %	4-7 Days %	8-14 Days %	15-30 Days %
Any ISR	90.2% (111/123)	18.9%	44.1%	36.9%	18.0%	30.6%	25.2%	26.1%
Swelling	87.8% (108/123)	36.1%	41.7%	22.2%	50.9%	33.3%	13.9%	1.9%
Tenderness	83.7% (103/123)	47.6%	35.9%	16.5%	52.4%	27.2%	16.5%	3.9%
Firmness	80.5% (99/123)	39.4%	39.4%	21.2%	39.4%	22.2%	25.3%	13.1%
Lumps/Bumps	79.7% (98/123)	41.8%	39.8%	18.4%	39.8%	22.4%	15.3%	22.4%
Bruising	77.2% (95/123)	36.8%	43.2%	20.0%	40.0%	43.2%	16.8%	0%
Pain	72.4% (89/123)	44.9%	47.2%	7.9%	68.5%	15.7%	12.4%	3.4%
Redness	69.9% (86/123)	48.8%	37.2%	14.0%	62.8%	29.1%	7.0%	1.2%
Discoloration	30.9% (38/123)	60.5%	31.6%	7.9%	76.3%	21.1%	2.6%	0%
Itching	26.0% (32/123)	50.0%	46.9%	3.1%	71.9%	18.8%	6.3%	3.1%

<sup>a</sup> N denotes the number of subjects who recorded responses in the diaries after repeat treatment.

<sup>b</sup> Maximum severity reported in the diary. The percentages by severity are based on the number of subjects with the corresponding injection site response.

<sup>c</sup> Maximum duration reported in the diary. The percentages by duration are based on the number of subjects with the corresponding injection site response.

ISRs that lasted beyond the 30-day diaries were considered adverse events (AEs). AEs were also reported by the Evaluating Investigator at follow-up visits. After initial treatment (or touch-up treatment, if performed), treatment-related AEs were reported in 50.6% (85/168) of subjects treated with JUVÉDERM VOLBELLA® XC and 51.8% (29/56) of subjects treated with control. The severity and duration of treatment-related AEs reported by > 5% of subjects after initial treatment (or touch-up treatment) are summarized in Table 4 and Table 5. All AEs with an incidence > 5% were treatment-related.

Most subjects treated with JUVÉDERM VOLBELLA® XC experienced mild (42.3%, 71/168) or moderate (17.9%, 30/168) treatment-related AEs. Similar results were observed after treatment with control (41.1% [23/56] and 23.2% [13/56] of subjects experienced mild and moderate AEs, respectively). Regardless of treatment group, the treatment-related AEs generally required no action to be taken and resolved without sequelae.

**Table 4. Treatment-Related Adverse Events by Severity After Initial Treatment  
Occurring in > 5% of Treated Subjects**

Adverse Event	JUVÉDERM VOLBELLA® XC (N = 168)				Control (N = 56)			
	Subjects <sup>a</sup>	Mild <sup>a</sup>	Moderate <sup>a</sup>	Severe <sup>a</sup>	Subjects <sup>a</sup>	Mild <sup>a</sup>	Moderate <sup>a</sup>	Severe <sup>a</sup>
Injection Site Mass	32.7%	26.8%	4.8%	1.2%	26.8%	17.9%	5.4%	3.6%
Injection Site Bruising	17.9%	10.7%	7.1%	0%	19.6%	10.7%	8.9%	0%
Injection Site Pain	11.9%	7.7%	4.2%	0%	21.4%	8.9%	8.9%	3.6%
Injection Site Induration	8.9%	7.7%	0.6%	0.6%	7.1%	3.6%	3.6%	0%
Injection Site Swelling	8.3%	4.8%	3.6%	0%	12.5%	3.6%	3.6%	5.4%
Injection Site Dryness	4.2%	3.0%	1.2%	0%	5.4%	1.8%	3.6%	0%

<sup>a</sup> The percentages are based on the number of subjects who received treatment with the corresponding product.

**Table 5. Treatment-Related Adverse Events by Duration After Initial Treatment  
Occurring in > 5% of Treated Subjects**

Adverse Event	JUVÉDERM VOLBELLA® XC						Control					
	Events % (n/N)	≤ 7 Days <sup>a</sup> %	8-14 Days <sup>a</sup> %	15-30 Days <sup>a</sup> %	> 30 Days <sup>a</sup> %	Not yet Resolved <sup>a</sup> %	Events % (n/N)	≤ 7 Days <sup>a</sup> %	8-14 Days <sup>a</sup> %	15-30 Days <sup>a</sup> %	> 30 Days <sup>a</sup> %	Not yet Resolved <sup>a</sup> %
Injection Site Mass	29.2% (101/346)	5.0%	1.0%	14.9%	76.2%	3.0%	26.1% (29/111)	10.3%	3.4%	3.4%	69.0%	13.8%
Injection Site Bruising	15.9% (55/346)	52.7%	2.9%	14.5%	3.6%	0%	18.0% (20/111)	60.0%	30.0%	10.0%	0%	0%
Injection Site Pain	12.1% (42/346)	50.0%	9.5%	4.8%	35.7%	0%	18.9% (21/111)	85.7%	9.5%	0%	4.8%	0%
Induration Site Induration	12.4% (43/346)	0%	4.7%	0%	95.3%	0%	6.3% (7/111)	0%	0%	0%	100%	0%
Injection Site Swelling	9.2% (32/346)	43.8%	18.8%	6.3%	31.3%	0%	15.3% (17/111)	64.7%	0%	11.8%	23.5%	0%
Injection Site Dryness	3.8% (13/346)	0%	46.2%	0%	53.8%	0%	4.5% (5/111)	60.0%	0%	40.0%	0%	0%

<sup>a</sup> The percentages by duration are based on the number of events for the corresponding treatment-related adverse event.

Treatment-related AEs after initial treatment (or touch-up treatment) occurring in ≤ 5% of subjects included chapped lips, dizziness, dry lips, general physical condition abnormal, headache, lip disorder (lumps), lip injury, oral herpes, presyncope, wound, and injection site discoloration, discomfort, edema, erythema, exfoliation, hyperaesthesia, hypoaesthesia, laceration, nodule, papule, paraesthesia, pruritus, and reaction.

In the clinical study, 8 subjects had lumps/bumps or swelling that occurred weeks to months after treatment. All of these AEs were mild or moderate. Swelling was treated with acetaminophen or doxycycline, and no treatment was given for the lumps/bumps. All of these events resolved without sequelae.

In the JUVÉDERM VOLBELLA® XC group, after repeat treatment with JUVÉDERM VOLBELLA® XC, treatment-related AEs were reported in 13.7% (17/124) of subjects. Injection site mass occurred in 7.3% (9/124) of subjects. Treatment-related AEs occurring in ≤ 5% of subjects included chapped lips and injection site bruising, edema, induration, and pain. Treatment-related AEs after repeat treatment occurred with lower incidence rates, severity, and duration compared to initial/touch-up treatment.

There were no treatment-related serious adverse events reported.

Lip safety assessments such as lip texture, functional features of the lips, lip sensitivity and sensation, Tyndall, and speech and articulation were evaluated at the screening visit and throughout the study. None of the lip assessments were remarkable or presented any safety concerns after treatment with either JUVÉDERM VOLBELLA® XC or control. On the validated *Recovery Early Life Impact* module of the FACE-Q questionnaire, subject reports showed that treatment with JUVÉDERM VOLBELLA® XC (mean score of 81.1) was significantly less disruptive to normal daily activities than treatment with control (mean score of 73.1).

## **B. European Clinical Study**

In a prospective, randomized, multicenter study, 280 subjects desiring lip volume enhancement were randomized 1:1 to receive treatment with JUVÉDERM VOLBELLA® XC or control. The subjects returned to the investigational sites at quarterly intervals for follow-up evaluations with the Treating Investigator. Subjects could receive repeat treatment with JUVÉDERM VOLBELLA® XC at months 6, 9, or 12 if the Investigator determined that the subject's Allergan Lip Fullness Scale (LFS) score had returned to baseline, or at month 12 if the subject's LFS score was lower than the treatment goal as assessed by the Investigator. At 1 month after repeat treatment, subjects returned for a final follow-up visit and were then exited from the study.

Common and expected ISRs were collected via 30-day diaries after each treatment. The incidence, severity, and duration of ISRs for subjects treated with JUVÉDERM VOLBELLA® XC after initial treatment are shown in Table 6. Most subjects reported an ISR after treatment, with the most common being swelling, tenderness, and firmness. The majority of ISRs were mild to moderate in severity and resolved within 14 days. The incidence of ISRs after touch-up treatment was lower than that after initial treatment. The ISRs after repeat treatment were similar to those after initial treatment.



**Table 6. Injection Site Responses by Severity and Duration After Initial Treatment with JUVÉDERM VOLBELLA® XC Occurring in > 5% of Treated Subjects**

Injection Site Response	Total % (n/N <sup>a</sup> )	Severity <sup>b</sup>			Duration <sup>c</sup>			
		Mild %	Moderate %	Severe %	1-3 Days %	4-7 Days %	8-14 Days %	15-30 Days %
Any ISR	95.5% (126/132)	17.5%	50.0%	32.5%	23.8%	28.6%	26.2%	21.4%
Swelling	90.9% (120/132)	31.7%	46.7%	21.7%	52.5%	40.8%	5.8%	0.8%
Tenderness	87.1% (115/132)	49.6%	42.6%	7.8%	57.4%	27.8%	10.4%	4.3%
Firmness	82.6% (109/132)	46.8%	38.5%	14.7%	45.9%	24.8%	18.3%	11.0%
Bruising	78.0% (103/132)	35.9%	41.7%	22.3%	35.0%	48.5%	15.5%	1.0%
Lumps/Bumps	76.5% (101/132)	37.6%	49.5%	12.9%	35.6%	25.7%	17.8%	20.8%
Redness	76.5% (101/132)	54.5%	38.6%	6.9%	73.3%	19.8%	6.9%	0%
Pain	68.9% (91/132)	50.5%	44.0%	5.5%	80.2%	16.5%	3.3%	0%
Itching	21.2% (28/132)	64.3%	25.0%	10.7%	82.1%	14.3%	3.6%	0%
Discoloration	17.4% (23/132)	65.2%	30.4%	4.3%	73.9%	21.7%	0%	4.3%

<sup>a</sup> N denotes the number of subjects who recorded responses in the diaries after initial treatment.

<sup>b</sup> Maximum severity reported in the diary. The percentages by severity are based on the number of subjects with the corresponding injection site response.

<sup>c</sup> Maximum duration reported in the diary. The percentages by duration are based on the number of subjects with the corresponding injection site response.

ISRs lasting beyond the 30-day diaries were considered AEs. AEs were also reported by the Investigator at follow-up visits. Among the 139 subjects treated with JUVÉDERM VOLBELLA® XC at the initial treatment, 14 (10.1%) experienced a total of 22 treatment-related AEs. The most common treatment-related AE was injection site mass (lumps/bumps). Subjects treated with JUVÉDERM VOLBELLA® XC experienced mild (7.9%, 11/139) or moderate (2.9%, 4/139) treatment-related AEs. In general, the treatment-related AEs required no action and resolved without sequelae.

Among the 139 subjects who were treated with JUVÉDERM VOLBELLA® XC at initial treatment and received repeat treatment with JUVÉDERM VOLBELLA® XC, 3 experienced a total of 4 treatment-related AEs after repeat treatment. These AEs include 3 reports of injection site mass and 1 report of oral herpes. None required treatment. Of the 4 AEs, 2 were mild (1 injection site mass [lumps/bumps] and 1 oral herpes), which resolved without sequelae, and 2 were reported with a maximum severity of severe (both events were injection site mass [lumps/bumps] in 1 subject) and then mild at the completion of the study.

## **C. Postmarket Surveillance**

The following reported adverse events were received from postmarket surveillance on the use of JUVÉDERM VOLBELLA® XC for lip augmentation outside the United States and were not observed in the clinical study. These adverse events, with a frequency of 5 events or more, are listed in order of prevalence: inflammatory reaction, loss/lack of correction, hematoma, allergic reaction, infection, paresthesia, herpes, migration, angioedema, and necrosis.

In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, antihistamines, anti-viral, arnica, drainage, hyaluronidase, ice, laser treatment, massage, NSAIDs, steroids, and warm compress. Outcomes for these reported events ranged from resolved to ongoing at the time of last contact.

In addition, two reports of blurry vision after injection into the periorbital area were received from postmarket surveillance for JUVÉDERM VOLBELLA® XC used outside of the United States. Reported treatment included anti-inflammatories. The outcomes for these two reports were either ongoing or unknown at time of last contact (see WARNINGS section).

Adverse reactions should be reported to Allergan Product Surveillance Department at 1-877-345-5372.

## **7. CLINICAL STUDIES**

### **A. Pivotal Study of JUVÉDERM VOLBELLA® XC**

#### **Pivotal Study Design**

A prospective, double-blind, randomized, controlled, multicenter clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM VOLBELLA® XC versus control for injection into the lips and perioral area (vermillion, vermillion border, philtral columns, Cupid's Bow, perioral lines, and/or oral commissures) for lip augmentation and the correction of perioral rhytids. A total of 224 subjects were randomized and underwent treatment with either JUVÉDERM VOLBELLA® XC (N = 168) or control (N = 56) at the outset of the study. An optional touch-up treatment was performed approximately 1 month after the initial treatment, if deemed necessary to achieve optimal correction.

The follow-up period consisted of safety and effectiveness follow-up visits at 1, 3, 6, 9, and 12 months after the last treatment. Subjects were then eligible for a repeat treatment with JUVÉDERM VOLBELLA® XC, with post-treatment follow-up for 1 month after repeat treatment, at which time all subjects completed the study.

#### **Study Endpoints**

The primary effectiveness measure for the study was the analysis of non-inferiority of JUVÉDERM VOLBELLA® XC relative to control in terms of change from baseline to month 3 in mean lip fullness based on Evaluating Investigator assessments using the validated 5-point Allergan Lip Fullness Scale (LFS).

Secondary measures included Evaluating Investigators' assessment of subjects' perioral lines using the validated Perioral Lines Severity Scale (POLSS) and subjects' satisfaction with their lips using the validated *Satisfaction with Lips* module of the FACE-Q questionnaire.

Additional effectiveness measures included Evaluating Investigators' assessments of subjects' upper and lower lip fullness using the LFS, perioral lines severity at maximal contraction using the Perioral Lines at Maximal Contraction (POLM) scale, oral commissures severity using the Oral Commissures Severity Scale (OCSS), global aesthetic improvement using the Global Aesthetic Improvement Scale (GAIS), and assessment of lip smoothness. Subjects performed self-assessments of lip lines (using the *Lip Lines* module of the FACE-Q questionnaire), lip hydration, and natural look and feel of the lips. The Treating Investigators also assessed injection ease and product moldability.

Safety measures included incidence, severity, and duration of ISRs and AEs, subjects' assessments of procedural pain and of impact to daily activities using the *Recovery Early Life Impact* module of the FACE-Q questionnaire, and Evaluating Investigators' assessments of Tyndall effect, lip sensation, features of the lip, and changes in pronunciation.

### **Subject Demographics**

Subject demographics and pretreatment characteristics of the JUVÉDERM VOLBELLA® XC and control groups are presented in Table 7.

**Table 7. Subject Demographics and Pretreatment Characteristics (N = 224)**

	<b>JUVÉDERM VOLBELLA® XC</b>	<b>Control</b>
	<b>(N = 168)</b>	<b>(N = 56)</b>
	<b>% (n/N)</b>	<b>% (n/N)</b>
<b>Gender</b>		
Female	97.6% (164/168)	94.6% (53/56)
Male	2.4% (4/168)	5.4% (3/56)
<b>Age</b>		
Median	53	55
Range	22-78	23-75
<b>Race</b>		
Caucasian	85.7% (144/168)	87.5% (49/56)
African-American	8.9% (15/168)	10.7% (6/56)
Asian	1.8% (3/168)	1.8% (1/56)
American Indian or Alaska Native	1.2% (2/168)	0% (0/56)
Other	2.4% (4/168)	0% (0/56)
<b>Fitzpatrick Skin Type</b>		
I/II	40.5% (68/168)	37.5% (21/56)
III/IV	47.0% (79/168)	50.0% (28/56)
V/VI	12.5% (21/168)	12.5% (7/56)
<b>Baseline Overall Lip Fullness (LFS) Score</b>		
Very Marked	0% (0/168)	0% (0/56)
Marked	1.8% (3/168)	5.4% (3/56)
Moderate	35.1% (59/168)	26.8% (15/56)
Mild	43.5% (73/168)	48.2% (27/56)
Minimal	19.6% (33/168)	19.6% (11/56)

**Treatment Characteristics**

The overall total median volume of JUVÉDERM VOLBELLA® XC injected to achieve optimal outcomes was 2.6 mL. Subjects received a median volume of 1.0 mL in the upper lip, 0.8 mL in the lower lip, 0.3 mL in the perioral lines, 0.5 mL in the oral commissures, and 0.1 mL in the philtral columns. Injection volumes into the lips and perioral area after repeat treatment tended to be lower, with the typical total median injection volume to achieve optimal correction after repeat treatment being approximately 1.6 mL. Similar injection volumes were used in subjects treated with the control device.

In general, injections into the vermilion body of the upper and lower lip were subdermal, and injections into the vermilion border, Cupid's bow, philtral columns, perioral lines, and oral commissures were intradermal. A tunneling technique, serial puncture technique, fanning technique, or combination was used to achieve optimal results.

**Effectiveness Results**

The primary endpoint of the study was met. The mean change from baseline to month 3 on the Allergan Lip Fullness Scale (LFS) was 1.1 for subjects treated with JUVÉDERM VOLBELLA® XC and 1.0 for subjects treated with control, with 80.3% (122/152) of subjects treated with JUVÉDERM VOLBELLA® XC

and 70.8% (34/48) of subjects treated with control showing a  $\geq 1$ -point improvement in overall lip fullness.

Throughout the follow-up period, JUVÉDERM VOLBELLA® XC continued to provide a clinically significant improvement in lip fullness ( $\geq 1$ -point mean improvement on the LFS), with a majority of subjects treated with JUVÉDERM VOLBELLA® XC demonstrating improvement through 1 year (Table 8).

**Table 8. Effectiveness Results Through 1 Year**

	JUVÉDERM VOLBELLA® XC
	% (n/N)
<b>1 Month</b>	86.2% (131/152)
<b>3 Months</b>	80.3% (122/152)
<b>6 Months</b>	71.1% (106/149)
<b>9 Months</b>	65.1% (95/146)
<b>1 Year</b>	61.8% (76/123)

At 3 months, improvements in perioral lines severity at rest were observed in 65.4% (53/81) of subjects treated with JUVÉDERM VOLBELLA® XC. At 1 year, 66.2% (45/68) of subjects treated with JUVÉDERM VOLBELLA® XC maintained improvement in perioral lines severity at rest.

At 3 months, 96.1% (147/153) of subjects treated with JUVÉDERM VOLBELLA® XC reported improvement in satisfaction with their lips, based on the *Satisfaction with Lips* module of the FACE-Q questionnaire, with the mean score increasing from 38.5 at baseline to 76.5. At 1 year, 79.7% (98/123) of subjects reported improved satisfaction with their lips over baseline, with a mean score of 59.6.

Through 1 year in the JUVÉDERM VOLBELLA® XC group, improvements in upper and lower lip fullness were similar to the improvements seen in overall lip fullness. Subjects treated with JUVÉDERM VOLBELLA® XC in the perioral lines and oral commissures also saw improvement in perioral lines severity at maximal contraction and oral commissures severity through 1 year.

On the GAIS at 3 months, 92.9% (143/154) of subjects in the JUVÉDERM VOLBELLA® XC group were scored as “improved” or “much improved” in appearance. At 1 year, the percentage of subjects scored as “improved” or “much improved” was 58.5% (72/123) in the JUVÉDERM VOLBELLA® XC group.

At 1 year, 74.8% (92/123) of subjects treated with JUVÉDERM VOLBELLA® XC reported improvement in satisfaction with their lip lines based on the *Satisfaction with Lip Lines* module of the FACE-Q, with the mean score increasing from 37.5 at baseline to 56.3.

#### **Follow-up After Repeat Treatment**

Repeat treatment with JUVÉDERM VOLBELLA® XC was administered to 124 subjects in the JUVÉDERM VOLBELLA® XC randomization group. The effectiveness profile after repeat treatment was similar to that after initial treatment. At 1 month after repeat treatment, the responder rate was similar to that after initial treatment, with 94.3% (115/122) of subjects showing at least a 1-point improvement in lip fullness, based on the Evaluating Investigator assessment.

## 8. INSTRUCTIONS FOR USE

### A. To Attach Needle to Syringe

#### **STEP 1: Remove tip cap**

Hold syringe and pull tip cap off the syringe as shown in Figure A.

Figure A



#### **STEP 2: Insert needle**

Hold the syringe body and firmly insert the hub of the needle (provided in the JUVÉDERM package) into the LUER-LOK<sup>®</sup> end of the syringe.

#### **STEP 3: Tighten the needle**

Tighten the needle by turning it firmly in a clockwise direction (see Figure B) until it is seated in the proper position as shown in Figure C.

Figure B

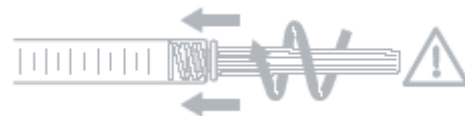
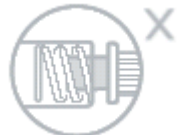


Figure C



Figure D



#### **STEP 4: Remove the needle cap**

Hold the syringe body in one hand and the needle cap in the other. Without twisting, pull in opposite directions to remove the needle cap as shown in Figure E.

Figure E



### B. Health Care Professional Instructions

1. JUVÉDERM VOLBELLA<sup>®</sup> XC injectable gel is a highly cross-linked, soft, smooth gel formulation that can be injected using a fine gauge (e.g., 30-G) needle into the lips and perioral area to add fullness and improve the shape of the lips, and to smooth perioral rhytids.
2. Prior to treatment, the patient's medical history should be obtained, and the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses,

adverse reactions, and method of administration. Patients also should be advised that supplemental “touch-up” treatments may be required to achieve and maintain maximum correction.

3. The patient’s treatment goals should be characterized with regard to proper proportion of upper and lower lip, vertical height, horizontal length, vermilion fullness, contouring of the vermilion border, Cupid’s bow, and philtral columns, as well as perioral lip rhytids and oral commissures. Pretreatment photographs are recommended.
4. Supplementary anesthesia may be used for additional pain management during and after injection.
5. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or other antiseptic. Prior to injecting, depress the plunger rod until the product flows out of the needle.
6. After the first small amount of material has been injected into the patient, wait a full 3 seconds to allow the lidocaine to take effect before proceeding with the rest of the injection.
7. The injection technique may vary with regard to the angle and orientation of the bevel, the depth of injection, and the quantity administered. A tunneling technique, serial puncture technique, fanning technique, or a combination has been used to achieve optimal results. Injecting the product too superficially may result in visible lumps and/or discoloration.
8. Inject JUVÉDERM VOLBELLA® XC by applying slow and even pressure on the plunger rod. It is important that the injection be stopped before the needle is pulled out of the skin to prevent material from leaking out or being placed too superficially in the skin.
9. If the needle is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle.
10. The typical volume injected into the lips and perioral area to achieve optimal correction was approximately 2.6 mL, which may vary depending on the goals the patient wishes to achieve. Injection volumes into the lips and perioral area after repeat treatment tended to be lower, with the typical total injection volume to achieve optimal correction being approximately 1.6 mL.
11. Correct to 100% of the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated defects may be difficult to correct.
12. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for

Dermatologic Surgery guidelines, which include hyaluronidase injection.<sup>1</sup>

13. When injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If overcorrection occurs, massage the area between your fingers or against an underlying superficial bone/teeth to obtain optimal results.
14. With patients who have localized swelling, the degree of correction is sometimes difficult to judge at the time of treatment. In these cases, it is better to invite the patient back to the office for a touch-up treatment.
15. After the initial treatment, an additional touch-up treatment may be necessary to achieve the desired level of correction. If further treatment is needed, the same procedure should be repeated until a satisfactory result is obtained. The need for an additional treatment may vary from patient to patient and is dependent upon a variety of factors such as treatment goals, lip fullness, perioral lines severity, skin elasticity, and dermal thickness at the treatment site.
16. Patients may have mild to moderate injection site responses after treatment in the lips and perioral area, which typically resolve within 14 days. Ice may be applied for a brief period following treatment to minimize swelling and reduce pain.
17. The health care professional should instruct the patient to promptly report to her/him any evidence of problems possibly associated with the use of JUVÉDERM VOLBELLA® XC.

### **C. Patient Instructions**

It is recommended that the following information be shared with patients:

- Within the first 24 hours, patients should avoid strenuous exercise, extensive sun or heat exposure, and alcoholic beverages. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the injection sites.
- To report an adverse reaction, phone the Allergan Product Support Department, 1-877-345-5372.

## **9. HOW SUPPLIED**

JUVÉDERM VOLBELLA® XC injectable gel is supplied in individual treatment syringes with 30-G needles for single-patient use and ready for injection (implantation). The volume in each syringe is as stated on the syringe label and on the carton. The contents of the syringe are sterile and non-pyrogenic. Do not resterilize. Do not use if package is opened or damaged.

## **10. SHELF LIFE AND STORAGE**

JUVÉDERM VOLBELLA® XC injectable gel must be used prior to the expiration date printed on the

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<sup>1</sup> Alam M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers. *Dermatol Surg.* 2008;34(suppl 1):S115-S148.



label.

Store at room temperature (up to 25°C/77°F). DO NOT FREEZE.

JUVÉDERM VOLBELLA® XC injectable gel has a clear appearance. In the event that a syringe contains material that is not clear, do not use the syringe; notify Allergan Product Support immediately at 1-877-345-5372.

To place an order, contact Allergan at 1-800-377-7790.

[Allergan Logo]  
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